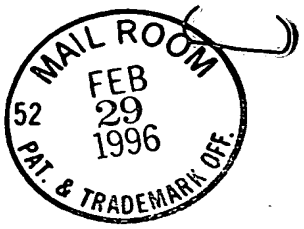
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



IN RE Application of
Dolors FERNANDEZ FORNER
et al Serial No.
08/437,682 filed 9 May
1995 for "New Indol
Derivatives"

DECLARATION

I, José M. Palacios, declare:

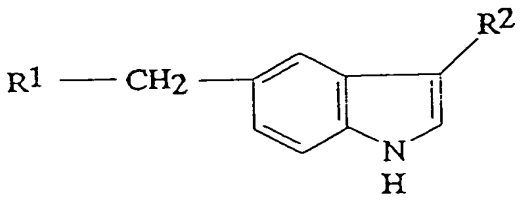
1. That I am a citizen of Spain, of c/o Laboratorios Almirall S.A., Research & Development Department, Cardener 68-74, 08024 Barcelona, Spain. I obtained a degree in Chemistry in 1970 from the University of Zaragoza, Spain, and Ph.D. (Doctor in Chemical Sciences) in 1976 from the Autonomous University of Barcelona, Spain. I trained as a Postdoctoral Fellow at the Neurobiology Laboratory of INSERM, France, from 1976 to 1978, and at the Pharmacology and Neuroscience Department of the Medical School, John Hopkins University, Baltimore, Maryland, United States of America, from 1978 to 1981. From August 1981 to September 1991 I worked as Laboratory Head at the CNS group, Preclinical Research of Sandoz Pharma, Ltd in Basel, Switzerland. From September 1991 to the present I have been the Director of Research and Development at Laboratorios Almirall S.A., the Assignee of the present application Serial no. 08/437,682. I am a member of several scientific societies in the pharmacology and neuroscience fields, as well as a member of the Editorial Boards of several International Scientific Journals in the same areas. I have published more than 300 papers in refereed International Scientific Journals and jointly authored books in these fields.

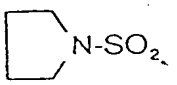
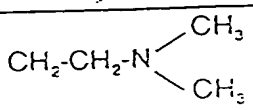
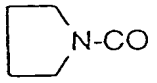
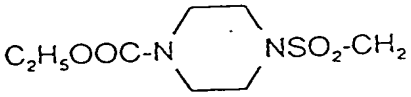
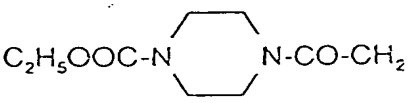
2. That I have read the specification of Serial no. 08/437,682, the official action dated 9 December 1994 and the Preliminary Amendment dated 17 October 1995 filed on the parent application Serial no. 08/211,446. I am fully conversant with the English Language.

3. That under my supervision the comparative test discussed in the Preliminary Amendment dated 17th October 1995 was carried out. The same tests set out on pages 3 to 5 of the specification of Serial no. 08/437,682 were carried out for the two compounds set forth in the Bays et al. reference (GB-A-2,082,175) which have a carbonyl group linking the indole alkyl residue and nitrogen hetero rings. These compounds were chosen to provide binding results that could be directly compared with the binding results of compounds 1 and 11 as defined in Table 2 on page 9 of the specification of Serial no. 08/437,682.

Thus the compounds chosen are identical to compounds 1 and 11 of the present invention, except for the replacement of the SO_2 group by a CO group.

4. That the results obtained are set forth in the Table below, in which the results for compounds 1 and 11 are repeated for convenience. The results for compounds 1 and 11 are taken from Table 1 on page 5 of the specification of Serial no. 08/437,682, and include the connection to the data obtained for compound 11 made in the Preliminary Amendment dated 17 October 1994.



Compound	R^1	R^2	M.P. °C	^{125}I-GT1	3H-8-OH-DPAT	5-HT_{1A} / 5-HT_{1D}
Compound 1			218-20(*)	10.7	825	77.1
Bays A		"	156-7(**)	88	503	5.7
Compound 11		"	170-1	3.2	850	265.6
Bays B		"	135-7	48	669	13.9

(*) Hydrochloride (**) Hydrogen fumarate

5. That by comparing compound 1 with compound A of Bays et al., it can clearly be seen that the substitution of the CO group of Bays et al. with an SO_2 group in accordance with the instant invention leads to a dramatic and unexpected increase in the 5-HT_{1A}/5-HT_{1D} IC_{50} ratio from 5.7:1 to 77.1:1. Similarly, a corresponding substitution for compound 11 and the Bays et al. compound B provides an increase in the ratio of from 13.9:1 to 265.6:1. I

believe that these considerable increases in the $5\text{-}HT_{1A}/5\text{-}HT_{1D}$ IC_{50} ratios could not have been foreseen from either the Bays et al. or Oxford et al. (EP-A-2,082,175) references. In fact, in my view Bays et al. teaches nothing as to the use of a sulfonyl group instead of a carbonyl group to link the indole alkyl residue and the nitrigen hetero ring. Further, Oxford et al. merely mentions that in their compounds the group represented by "D" could be either -CO- or $-SO_2-$. Oxford appears to treat the CO and SO_2 groups as equivalents and makes no mention of any functional differences between the two. Oxford et al. provides no teaching, nor does it mention that the substitution of the CO for the SO_2 groups in compounds such as those of Bays et al. would produce dramatic changes in the binding affinity of said compounds for the $5\text{-}HT_{1A}$ and $5\text{-}HT_{1D}$ receptors.

6. The Undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of title 18 of the United States Code, and that a wilful false statement may jeopardise the validity of the Application or any patent issuing thereon.

Dated this 7 day of February 1996

José M. Palacios